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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* DAVID F. MUIR

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Appeal 2009-004524
Application 10/812,776
Technology Center 1600

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Decided: November 2, 2009

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Before TONI R. SCHEINER, DONALD E. ADAMS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

## DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods for preparing nerve grafts for implantation. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

*Statement of the Case*

*Background*

"Peripheral nerve injuries are a major source of chronic disability" (Spec. 1, l. 18). The Specification notes that "[n]erve grafting is warranted with nerve ablation but presents several practical challenges" (Spec. 2, ll. 22-23).

*The Claims*

Claims 1, 6-23, 30-40, 42-56, and 117-123 are on appeal. We will focus on independent claims 1 and 38, which are representative and read as follows:

> 1. A method for preparing a nerve graft suitable for subsequent implantation, the method comprising:
>
> degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan of a nerve graft comprising a nerve tissue segment while maintaining an intact basal lamina tube structure of the nerve graft, thereby enhancing post-implantation axonal traversal of an interface between the nerve graft and host nerve tissue relative to a nerve graft in which chondroitin sulfate proteoglycan was not degraded; and
>
> rendering the nerve graft acellular by killing cells in the nerve graft.
>
> 38. A method for enhancing the regenerative potential of a nerve graft suitable for subsequent implantation, the method comprising:
>
> degrading, by in vitro culturing, chondroitin sulfate proteoglycan of a nerve graft comprising a nerve tissue segment while maintaining an intact basal lamina tube structure of the nerve graft, thereby enhancing post-

> implantation axonal traversal of an interface between the nerve graft and host nerve tissue relative to an a nerve graft in which chondroitin sulfate proteoglycan was not degraded, wherein culturing conditions comprise a temperature within the range of about 10° C to about 37° C for a period of time within the range of about 24 hours to about 96 hours; and
>
> rendering the nerve graft acellular by killing cells in the nerve graft

*The prior art*

The Examiner relies on the following prior art references to show unpatentability:

Dennis US 6,448,076 B2 Sep. 10, 2002

La Fleur et al., *Basement Membrane and Repair of Injury to Peripheral Nerve: Defining a Potential Role for Macrophages, Matrix Metalloproteinases, and Tissue Inhibitor of Metalloproteinases-1*, 184 J. OF EXPERIMENTAL MEDICINE 2311-2316 (December 1996).

Lassner et al., *Preservation of Peripheral Nerve Grafts: A Comparison of Normal Saline, HTK Organ Preservation Solution, and DMEM Schwann Cell Culture Medium*, 11(6) J. OF RECONSTRUCTIVE MICROSURGERY 447-453 (November 1995).

Evans et al., *The Peripheral Nerve Allograft: A Comprehensive Review of Regeneration and Neuroimmunology*, 43 PROGRESS IN NEUROBIOLOGY 187-233 (1994).

Ide et al., *Schwann Cell Basal Lamina and Nerve Regeneration*, 288 BRAIN RESEARCH 61-75 (1983).

*The issues*

A. The Examiner rejected claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 112, second paragraph as being indefinite (Ans. 3-4).

B. The Examiner rejected claims 1, 6-15, 17-21, 30-40, 42-51, 53-56, 117-120, 122, and 123 under 35 U.S.C. § 102(b) as being anticipated by La Fleur (Ans. 4-5).

C. The Examiner rejected claims 1, 6-15, 17-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 102(b) as being anticipated by Lassner (Ans. 5-6).

D. The Examiner rejected claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122, and 123 under 35 U.S.C. § 102(e) as being anticipated by Dennis (Ans. 6-7).

E. The Examiner rejected claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 103(a) as being obvious over Dennis, La Fleur, Ide, and Evans (Ans. 7-9).

*A. 35 U.S.C. § 112, second paragraph*

The Examiner rejected claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 112, second paragraph as being indefinite (Ans. 3-4).

The Examiner finds that "[t]he limitations such as 'degrading CSPG' and 'enhancing post-implantation' are the intended effects of 'in vitro culturing' as claimed" (Ans. 3-4). The Examiner finds that "[n]o specific treatment agents and/or conditions are recited in the claims. Thus, it is uncertain what 'degrading' and/or 'enhancing' treatments are encompassed in the method for preparing a nerve graft" (Ans. 4).

Appellant contends that the "active step recited in the claims is degrading CSPG. The step is not in vitro culturing, as alleged by the Examiner. The active degrading step recited in the claims is achieved by in vitro culturing-specific CSPG degradation, and not by any culturing procedure generally, as the Examiner mistakenly alleges" (App. Br. 7).

In view of these conflicting positions, we frame the definiteness issue before us as follows:

Did the Examiner err in finding that the terms "degrading CSPG" and "enhancing post-implantation" are indefinite?

*Findings of Fact (FF)*

1. Claim 1 requires that the "degrading" chondroitin sulfate proteoglycan step occur "by in vitro culturing" which will inherently function in "enhancing post-implantation axonal traversal" (*see* Claim 1).

2. The Specification teaches that

> [t]he culture methods of the subject invention involve "predegenerating" the nerve tissue in vitro, which, following engraftment, improves the ability of regenerating axons to traverse the interface between the graft and host nerve tissue. Without being bound by theory, the culturing methods of the subject invention allow the living nerve cells to express CSPG-degrading enzymes and promote Schwann cell proliferation

(Spec. 27, ll. 17-22).

3. The Specification teaches that "culture of nerve explants, using conditions to support cell viability and growth, allows for cell-mediated degeneration and significantly enhances the regenerative potential of nerve grafts" (Spec. 56, ll. 17-19).

*Principles of Law*

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

During examination of a patent application, pending claims are given their broadest reasonable construction consistent with the specification. *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). However, the fact that a claim is broad does not mean that it is indefinite, that is, undue breadth is not indefiniteness. *In re Johnson*, 558 F.2d 1008, 1016 n.17 (CCPA 1977).

*Analysis*

The Examiner argues that the "definitions are rather broad . . . and they do not clearly point out any specific parameters for the culture conditions during the culturing step" (Ans. 10).

We are not persuaded by the Examiner's argument that because the terms are broad, the words are indefinite. The Examiner is equating the breadth of the claim with indefiniteness. However, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971). The Examiner has not identified any element of the claim which would be ambiguous to the ordinary artisan, who understands the word "culturing", particularly in light of the discussion in the Specification (*see, e.g.*, FF 2-3).

*Conclusion of Law*

The Examiner erred in finding that the terms "degrading CSPG" and "enhancing post-implantation" are indefinite.

We reverse the rejection of claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 112, second paragraph as being indefinite.

*B. 35 U.S.C. § 102(b) over La Fleur*

The Examiner rejected claims 1, 6-15, 17-21, 30-40, 42-51, 53-56, 117-120, 122, and 123 under 35 U.S.C. § 102(b) as being anticipated by La Fleur (Ans. 4-5).

The Examiner finds that La Fleur teaches the "step of 'culturing' the nerve tissue in vitro in DMEM medium comprising various supplements at temperature 37°C for various periods of time" (Ans. 4). The Examiner finds that La Fleur teaches the "step of 'killing' the nerve tissue by chemical treatment for further extraction of proteins, RNA and other components" (Ans. 5).

Appellant argues that "La Fleur fails to teach or suggest a *method for preparing a nerve graft suitable for subsequent implantation*, because La Fleur simply is not concerned with and does not address this problem" (App. Br. 9). Appellant argues that use "of concentrated phenol is inconsistent with *preparing a nerve graft suitable for subsequent implantation*" (App. Br. 12).

In view of these conflicting positions, we frame the anticipation issue before us as follows:

Did the Examiner err in finding that the method of preparing nerve segments of La Fleur would inherently prepare "a nerve graft suitable for subsequent implantation"?

*Findings of Fact*

4. La Fleur teaches that "nerve segments (3 cm total) were weighed and placed in 500 ul DMEM supplemented with 0.2% lactalbumin hydrolysate" (La Fleur 2312, col. 2).

5. La Fleur teaches that "[n]erve segments were removed after incubation, rinsed in PBS, and placed in TRIzol reagent (GIBCO BRL) for RNA extraction and subsequent semi-quantitative reverse transcription (RT)-PCR" (La Fleur 2312, col. 2).

6. La Fleur teaches that "TIMP-1 and cytokine Mrna expression was upregulated in undamaged nerve explants incubated with medium conditioned by macrophages" (La Fleur 2311, abstract).

*Principles of Law*

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Analysis of whether a claim is patentable over the prior art under 35 U.S.C. § 102 begins with a determination of the scope of the claim. We determine the scope of the claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction in light of the specification as it would be interpreted by one of ordinary skill in the art. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). The properly interpreted claim must then be compared with the prior art.

"If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is 'inherent' in its disclosure." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* (*quoting Continental Can Co. v.*

*Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)) (internal quotation marks and citations omitted).

"[A] preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed.Cir.2002) (*quoting Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed.Cir.1999)). A preamble is not limiting, however, "'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.'" *Id.* (*quoting Rowe v. Dror*, 112 F.3d 473, 478 (Fed.Cir.1997)).

*Analysis*

Both of the independent claims require two steps, *in vitro* culturing a nerve graft and rendering the nerve graft acellular and both claims include a preamble which requires that the graft is "suitable for subsequent implantation" (*see* Claims 1 and 38).

We begin with claim construction, and determine whether the preamble requirement that the graft must be "suitable for subsequent implantation" is limiting in this instance. In this case, the phrase "suitable for subsequent implantation" is necessary to give meaning to the claim. This phrase imposes structural requirements that the nerve graft must satisfy after being subjected to the steps of the claimed process of claims 1 and 38. The central requirement of this phrase is that the graft is in a form which can be implanted into a patient, whether human or other animal, and which is not degraded, destroyed or incapable of implantation due to toxicity.

La Fleur reasonably teaches an *in vitro* culturing step which may be treating as inherently degrading the chondroitin sulfate proteoglycan (FF 4). La Fleur does not teach a step of rendering the nerve graft acellular which will result in a nerve graft that is "suitable for subsequent implantation" as required by claims 1 and 38.

While we agree with the Examiner that the nerve graft will be rendered acellular by La Fleur's treatment with TRIzol (FF 5), we are not persuaded by the Examiner's argument that "the reference clearly identifies the nerve segments, which were cultured and then chemically treated with Trisol reagent for RNA extraction . . . as 'undamaged' nerve explants" (Ans. 12).

This argument is simply incorrect. When La Fleur states that the nerve explants are undamaged, La Fleur is discussing the explants as undamaged prior to culture and TRIzol treatment, not after those treatments (*see* La Fleur 2311, abstract; FF 6).

The Examiner also argues that the "Trizol reagent is known to disrupt cells while maintaining integrity of cellular components" (Ans. 13). The Examiner provides no evidence to support this position and the teaching of La Fleur directly contradicts this statement. La Fleur teaches that the TRIzol treated tissue is subjected to RT-PCR without further processing, which is a method which requires the disruption of cells and the release of mRNA within the cells in order for the reverse transcription and amplification reactions to function, so that the integrity of cellular components cannot reasonably be maintained (*see* FF 5).

We also find unpersuasive the Examiner's argument that "it is quite reasonable to assume that one of skill in the art would rinse the tissue grafts before graft implantation in order to remove any toxic chemical reagents" (Ans. 13). Since La Fleur does not teach, suggest, or in any way contemplate using the TRIzol treated nerve grafts for any purpose other than as a source of mRNA for RT-PCR, there is *no* reason to assume that the resultant solution of La Fleur, containing whatever remnants exist of the nerve graft in TRIzol, would be rinsed to remove the TRIzol. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

*Conclusion of Law*

The Examiner erred in finding that the method of preparing nerve segments of La Fleur would inherently prepare "a nerve graft suitable for subsequent implantation."

We reverse the rejection of claims 1, 6-15, 17-21, 30-40, 42-51, 53-56, 117-120, 122, and 123 under 35 U.S.C. § 102(b) as being anticipated by La Fleur.

*C. 35 U.S.C. § 102(b) over Lassner*

The Examiner rejected claims 1, 6-15, 17-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 102(b) as being anticipated by Lassner (Ans. 5-6).

The Examiner finds that Lassner teaches a "step of culturing the nerve tissue segments in vitro under culture conditions including temperature permissive for cellular outgrowth or 37 °C, time 48 hours and DMEM

medium with serum" (Ans. 5). The Examiner finds that Lassner teaches a "step of killing the nerve tissue by freezing at minus 18 °C" (Ans. 5-6).

Appellant argues that Lassner's "activities do not represent in vitro culturing, as required by Appellant's claims. The cold, ischemic conditions are stasis conditions and do not promote physiological activity" (App. Br. 13). Appellant argues that "the use of methanol is not compatible with preparing a nerve graft for subsequent implantation" (App. Br. 14).

In view of these conflicting positions, we frame the anticipation issue before us as follows:

Did the Examiner err in finding that the method of preparing nerve segments of Lassner would prepare "a nerve graft suitable for subsequent implantation"?

*Findings of Fact*

7. Lassner teaches, in a first experiment, that a "2.5-cm segment was dissected and subjected to cold ischemia of 4°C in Schwann cell culture medium . . . Storage periods were 14, 32, 72, and 120 hr" (Lassner 148, col. 1).

8. Lassner teaches, in the first experiment, that "[n]egative controls were nerves subjected to repeated freeze and thawing to evacuate all viable cells. After the extracorporeal treatment, the nerves were reimplanted orthotopically" (Lassner 148, col. 2).

9. Lassner teaches, in a second experiment, that "nerves were harvested from adult Sprague-Dawley rats, as already described, and pre-treatment performed, according to the described experimental Groups" (Lassner 148, col. 2).

10. Lassner teaches that the nerves were "placed in 30-mm culture dishes containing 1 ml of Dulbecco's modified Eagle Medium . . . They were maintained at 5 percent $CO_2$/95 percent air for two days. Cellular outgrowth around the specimen was evaluated morphologically" (Lassner 148, col. 2).

11. Lassner teaches that the nerve "specimens were fixed with methanol at -18°C, incubated with the monoclonal antibody anti-S 100 . . . for 24hr, followed by an alcaline [sic alkaline] phosphatase conjugated secondary antibody . . . for 24 hr. Staining was performed according to the method previously described" (Lassner 148, col. 2 to 149, col. 1).

*Analysis*

While we agree with the Examiner that the culturing which resulted in cellular outgrowth satisfies the "culturing" step of claims 1 and 38, we think that Appellant has the better position regarding whether methanol results in a nerve graft which is "suitable for subsequent implantation" (Claim 1).

As the Examiner correctly notes, Lassner teaches, in the second experiment, treatment of nerves at a cold, but not freezing temperature, followed by culture which resulted in outgrowth of some nerve specimens (FF 7-10).

However, we are not persuaded by the Examiner's finding that "it is quite reasonable to assume that one of skill in the art would rinse the tissue grafts before graft implantation in order to remove any toxic chemical reagents" (Ans. 14). As above, the methanol treatment suggested by Lassner was not intended to kill the cells in preparation for nerve grafting, but was designed to fix the cells in preparation for immunohistologic

characterization (FF 11). Just as we discussed *supra* regarding TRIzol, the Examiner has not shown that methanol treated nerve grafts *may* be subsequently treated to permit implantation into animals, much less that the specific methanol and antibody treated nerve grafts of Lassner would reasonably be "suitable for subsequent implantation" and "necessarily function[] in accordance with, or include[], the claimed limitations." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002).

*Conclusion of Law*

The Examiner erred in finding that the method of preparing nerve segments of Lassner would prepare "a nerve graft suitable for subsequent implantation".

We reverse the rejection of claims 1, 6-15, 17-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 102(b) as being anticipated by Lassner.

*D. 35 U.S.C. § 102(e) over Dennis*

The Examiner rejected claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122, and 123 under 35 U.S.C. § 102(e) as being anticipated by Dennis (Ans. 6-7).

The Examiner finds that Dennis teaches a "step of culturing in vitro the nerve graft in a medium or in a balanced salt solution" (Ans. 6). The Examiner finds that Dennis teaches a "step of rendering the nerve graft acellular by chemical treatment" (Ans. 6-7).

Appellant argues that "Dennis' methods are not compatible with a method for preparing a nerve graft suitable for subsequent implantation as required by the Appellant's claims" (App. Br. 17). Appellant argues that "Dennis does not describe a selective degrading step by *in vitro* culturing. In

Dennis, the nerve is placed in PBS and then acellularization is carried out. There is no *in vitro* culturing" (App. Br. 15).

In view of these conflicting positions, we frame the anticipation issue before us as follows:

Did the Examiner err in finding that the method of preparing nerve segments of Dennis would comprises a step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan" as required by claims 1 and 38?

*Findings of Fact*

12. Dennis teaches "a method for chemically acellularizing a biological tissue sample, such as a peripheral nerve" (Dennis, col. 1, ll. 25-26).

13. Dennis teaches that "the tissue sample is harvested from a suitable donor, and then submersed in a balanced salt solution, such as Dulbecco's phosphate buffered saline" (Dennis, col. 2, ll. 40-42).

14. Dennis teaches that the "disrupting of cell membranes then includes submersing the biological tissue sample in a solution including glycerol, whereas denaturing and removing intracellular proteins includes submersing the biological tissue in at least one detergent solution" (Dennis, col. 2, ll. 43-47).

15. Dennis teaches that "the biological tissue sample is preferably rinsed with distilled water between each solution change. The resulting acellularized tissue construct can then be stored in a physiologic saline solution, and later implanted in a suitable recipient" (Dennis, col. 2, ll. 53-57).

16. The Specification teaches that the "method of *in vitro* culture involves culturing the nerve tissue under conditions that permit the nerve tissue to grow *in vitro* and increase the neurite-promoting activity of the nerve tissue when subsequently implanted as a graft" (Spec. 27, ll. 24-26).

*Analysis*

While we agree with the Examiner that Dennis teaches preparation of nerve grafts which chemically rendered acellular and which are "suitable for subsequent implantation" (*see, e.g.*, FF 12, 14, 15), we think that Appellant has the better position regarding whether Dennis teaches the step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan" as required by claims 1 and 38.

The Specification clearly teaches that the in vitro culture results in nerve tissues growing *in vitro* (FF 16). Dennis does not teach placement of the nerve grafts into any culture medium nor does Dennis teach culturing the nerve grafts prior to rendering the nerve grafts acellular. At best, Dennis teaches placement of the nerve grafts into phosphate buffered saline, which is not reasonably understood as a culture medium which would permit the nerve graft to grow (FF 13).

We find unpersuasive the Examiner's argument that "the final effects with regard to remodeling nerve tissue segment in vitro are considered to be the same as result of the same active step of 'in vitro culturing'" (Ans. 15). Even if the nerve grafts which result from the Dennis procedure were identical to those which result from the claimed procedure, a finding that the Examiner has not demonstrated, this argument would be irrelevant. The claims are method claims, not product or product-by-process claims. In

order to anticipate, Dennis must teach the claimed method steps, not other method steps which might result in the same product.

We also are not persuaded by the Examiner's argument that the claimed culturing step "encompasses temperature and time . . . that are common parameters for cell maintenance or cell culturing on a laboratory bench" (Ans. 15). While the claimed culturing step *is* generic, Dennis simply does not teach such a step and therefore does not anticipate.

*Conclusion of Law*

The Examiner erred in finding that the method of preparing nerve segments of Dennis would comprises a step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan" as required by claims 1 and 38.

We reverse the rejection of claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122, and 123 under 35 U.S.C. § 102(e) as being anticipated by Dennis.

*E. 35 U.S.C. § 103(a) over Dennis, La Fleur, Ide, and Evans*

The Examiner rejected claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 103(a) as being obvious over Dennis, La Fleur, Ide, and Evans (Ans. 7-9).

The Examiner finds that Dennis "teaches the use of PBS or physiological balanced salt solution for "culturing" or for pre-treatment before acellularization step" (Ans. 8). The Examiner finds that Dennis "lacks an explicit teaching about the use of an enriched cell culture media" (Ans. 8). The Examiner finds that La Fleur "teaches that incubation of nerve segments in complete cell culture medium with various supplements results in upregulation of TIMP-1 expression and that TIMP-1 protects basement

membrane of nerve tissue from uncontrolled disintegration or degradation after injury" (Ans. 8).

The Examiner finds it obvious to "substitute a supplemented culture medium for a buffered salt solution in two-step method" of Dennis "because culturing nerve tissues promotes up-regulation of compounds that remodel basement membrane of nerve tissues and protect from uncontrolled degradation after injury as adequately taught by La Fleur" (Ans. 9).

Appellant argues that "Dennis and La Fleur fail to describe *degrading, by in vitro culturing, CSPG of a nerve graft*" (App. Br. 19). Appellant also argues that "the methods of both Dennis and La Fleur result in grafts that are structurally different from grafts produced in accordance with the present claims, and also involve chemicals that simply are not compatible with a *method of preparing a nerve graft suitable subsequent implantation*" (App. Br. 19).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding a step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan" obvious over the teachings of Dennis, La Fleur, Ide, and Evans?

*Findings of Fact*

17. Ide teaches that a "small nerve segment about 7 mm long was excised from the distal portion of the transected sciatic nerve. It was treated 5 times by repetitive freezing and thawing" (Ide 62, col. 1).

18. Ide does not teach culturing the nerve segments (*see* Ide 62).

19. Evans does not teach culturing nerve segments (*see, e.g.*, Evans 222).

20. The Specification teaches that "specific members of the matrix metalloproteinase family, MMP-2 and MMP-9 . . . degrade the core protein of CSPG" (Spec. 5, ll. 20-21).

21. The Specification teaches that the "increase in neurite-promoting activity resulting from *in vitro* degeneration is attributed to a heightened expression and activation of MMP-2 by Schwann cells" (Spec. 56, ll. 1-3).

*Principles of Law*

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* at 417-18, *quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Examiner has the initial burden of establishing a prima facie

case obviousness under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) ("[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability.").

*Analysis*

While we agree with the Examiner that La Fleur does teach culturing the nerve grafts (FF 4) and Dennis teaches rendering the nerve grafts acellular (FF 12), there is no satisfactory reason to combine the disclosures of these two references, nor do the disclosures of Ide or Evans provide any reason to combine these concepts (FF 17-19).

In culturing the nerve grafts, La Fleur provides no reason why an ordinary practitioner would choose to culture the nerve segment and then implant into an animal (FF 4-6). Dennis provides no reason to culture the nerve segment at all, as discussed *supra*. The Examiner's stated reason, that incubation desirably upregulates TIMP-1, an inhibitor of matrix metalloproteinases (*see* Ans. 8) is flatly inconsistent with the requirements of claims 1 and 38. The claims require degradation of CSPG (*see* Claims 1 and 38). The Specification demonstrates that culturing results in upregulation of MMP-2 to cleave CSPG (FF 20-21). Upregulation of TIMP-1 would reasonably be expected to inhibit MMP-2 and thereby prevent the degradation of CSPG, which would yield the opposite result from that required by claims 1 and 38.

*Conclusion of Law*

The Examiner erred in finding a step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan" obvious over the teachings of Dennis, La Fleur, Ide, and Evans.

We reverse the rejection of claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 103(a) as being obvious over Dennis, La Fleur, Ide, and Evans (Ans. 7-9).

SUMMARY

In summary, we reverse the rejection of claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 112, second paragraph as being indefinite.

We reverse the rejection of claims 1, 6-15, 17-21, 30-40, 42-51, 53-56, 117-120, 122, and 123 under 35 U.S.C. § 102(b) as being anticipated by La Fleur.

We reverse the rejection of claims 1, 6-15, 17-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 102(b) as being anticipated by Lassner.

We reverse the rejection of claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122, and 123 under 35 U.S.C. § 102(e) as being anticipated by Dennis.

We reverse the rejection of claims 1, 6-23, 30-40, 42-56, and 117-123 under 35 U.S.C. § 103(a) as being obvious over Dennis, La Fleur, Ide, and Evans (Ans. 7-9).

REVERSED

dm

GOODWIN PROCTER LLP
PATENT ADMINISTRATOR

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